Current Review

Beta-blocker therapy and the risk of anaphylaxis

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Beta-blocker therapy is associated with an increase in the severity and, possibly, the incidence of acute anaphylaxis. The population at risk consists of people with allergic conditions who are given a β-blocker for an unrelated condition. Anaphylaxis under these conditions may be severe, protracted and resistant to conventional treatment because of the β-adrenergic blockade. Severe or fatal attacks have been triggered by insect stings, the ingestion of allergenic foods or drugs, and injections of radiocontrast media, antisera or immunotherapy antigens. These occurrences are probably infrequent, but their incidence is unknown. At least two fatal cases have recently occurred in Canada. Clinical allergists, internists and family practitioners in particular should be aware of the need for aggressive and prolonged support in patients who experience anaphylaxis while receiving β-blocker therapy and should report all such occurrences to the federal registry of adverse drug reactions. Allergy skin testing or immunotherapy is inadvisable in patients who take a β-blocker orally or in the form of ophthalmic eyedrops. The list of relative contraindications to β-blocker use should be extended to include susceptibility to recurrent anaphylaxis, whether it is idiopathic or due to an identifiable cause.

La thérapeutique par les β-bloquants s'accompagne d'une augmentation de la gravité et peut-être de la fréquence de l'anaphylaxie aiguë chez les sujets souffrant d'allergie qui prennent des β-bloquants pour d'autres raisons. C'est le blocage β-adrénergique lui-même qui rend compte de la gravité des accidents anaphylactiques, de leur plus grande durée et de leur résistance au traitement habituel. Une crise grave, parfois mortelle, a fait suite à une piqûre d'insecte, à l'ingestion d'un allergène alimentaire ou médicamenteux, et à l'injection d'une substance de contraste, d'un sérum antitoxique ou d'antigènes d'immunothérapie. La fréquence de ces faits est inconnue, mais on ne la croit pas élevée. Deux cas mortels ont été consignés récemment au Canada. Il revient surtout à l'allergiste, à l'interniste et au médecin de famille d'être conscients du besoin d'un traitement énergique et prolongé devant un tel accident et de signaler celui-ci au registre fédéral des réactions nocives aux médicaments. Le traitement aux β-bloquants par voie orale ou en gouttes oculaires contre-indique la pratique des cuti-réactions allergéniques et de l'immunothérapie. Il y a lieu d'ajouter à la liste des contre-indications relatives de l'emploi des β-bloquants la prédisposition à l'anaphylaxie, que celle-ci soit idiopathique ou de cause connue.

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A 58-year-old man with mild asthma experienced acute bronchospasm and shock after a routine immunotherapy injection for hay fever. The bronchospasm failed to respond to prompt, aggressive treatment by his family physician and the staff of a nearby hospital emergency department. The attack was complicated by bradycardia, cardiac arrest, persisting shock and hypoxemic encephalopathy.[1] After 6 days life-support systems were withdrawn.

The patient had also been taking a β-blocker, propranolol. The likelihood that the propranolol contributed to this unexpected death is suggested

by the growing number of case reports of severe anaphylactic reaction in patients receiving β-blocker therapy.[1-12] These reports suggest that such therapy may increase the incidence or severity of clinical anaphylaxis and interfere with the pharmacotherapeutic action of drugs normally useful for its emergency treatment.

These effects are distinguishable from the well-known bronchoconstrictor effects of low or conventional doses of β-blockers in patients with latent or clinically active asthma or chronic obstructive pulmonary disease[13-16] in that the anaphylactic attacks may occur in nonasthmatic subjects. They are also distinct from the hypertensive crises (with or without stroke) that may complicate the use of β-blockers along with sympathomimetic eyedrops or a nasal decongestant[17-19] and from poisoning due to excessively high β-blocker dosage.[20] Dermatitic or urticarial hypersensitivity reactions have occasionally been reported with β-blockers;[21] they pose no serious threat to the patient and reflect allergy to the drug. Anaphylactic attacks, on the other hand, reflect allergy to completely unrelated antigens to which the patient may accidentally be exposed.

Severe anaphylaxis has been reported in patients receiving β-blockers after the ingestion of allergenic foods,[3-5] orally given penicillin,[5,10] acetylsalicylic acid (ASA)[5] and nonsteroidal anti-inflammatory drugs,[5,11] insect stings[5,7,8] and the injection of immunotherapy antigens for hay fever,[1,3,4,6] radiocontrast media for diagnostic investigations[2,9,11,12] and heterologous antibody for the suppression of allograft rejection.[11] As in the patient I have described the attacks have been characterized by various combinations of profound hypotension, bradycardia with or without atrioventricular nodal block, severe sustained bronchospasm, and hives or angioedema, and they have been described as being unusually resistant to conventional treatment. Deaths have been reported, but the true death rate is unknown, since there is underreporting.[10] At least two deaths occurred in Canada in a recent 19-month period, one in a person who presented with persisting shock and angioedema of the upper airways and oropharynx triggered by an ASA-containing analgesic (Dr. Guérin Dorval, Royal Victoria Hospital, Montreal: personal communication, 1986) and the other as I have described. At the time of writing only one of these cases was documented in the Drug Adverse Reaction Reporting Program of the Health Protection Branch, Department of National Health and Welfare.

Pathogenesis

The endogenous production of histamine and other important mediators of anaphylaxis is normally inhibited by β-adrenergic neurohumoral mechanisms acting via adenosine 3′,5′-cyclic monophosphate (cyclic AMP), and it is stimulated by α-adrenergic and cholinergic mechanisms.[22] Beta-blockade perturbs the homeostatic balance of these controls, resulting in an increase in both the intracellular synthesis and the release of anaphylactic mediators.[23,24] Beta-blockade also enhances the responsiveness of the pulmonary, cardiovascular, skin and other systems to the mediators released[25-28] and increases the mortality of experimental anaphylaxis induced by immunologic[28] or nonimmunologic[27] mechanisms of mediator release. Finally, β-blockade increases the production of total IgE in atopic subjects and can reverse the normal inhibitory effect of immunotherapy on the production of specific IgE.[29]

The atopic diathesis present in about 20% of the general population may be a potential risk factor, since atopy has been reported to be associated with β_2-adrenergic hyporeactivity plus cholinergic hyperreactivity.[22,30] Patients with allergic asthma show excessive α-adrenergic responsiveness as well.[22,30] Further perturbation by β-blockers of this intrinsically unstable combination would be expected to augment local and systemic mediator release, particularly in those with atopic asthma, and thus increase the risk of clinical anaphylaxis.

"Selective" β-blockers such as metoprolol and atenolol tend to spare the β_2-receptors, which modulate smooth muscle tonus in the airways. However, the systemic release of mediators of anaphylaxis is under the control of adrenoreceptors that differ functionally from classic β_2-receptors in that they can be blocked by either β_1- or β_2-antagonists.[31,32] If these receptors are blocked, mediator synthesis and release are enhanced. Thus, it cannot be assumed that substitution of a "cardioselective" β-blocker will necessarily circumvent the potential risk of anaphylaxis. Indeed, in several of the reported cases a selective agent was involved (Dr. Guérin Dorval, Royal Victoria Hospital: personal communication, 1986).[33]

The degree of β-blockade achieved in a particular patient depends on the dosage used and on differences in individual susceptibility to β-blockade.[15] The latter may relate in part to intersubject variance in the pharmacokinetics of β-blockers.[34,35] Also, the fluctuating course of asthma and allergy, extraneous factors such as intercurrent viral infections and injection of a viral vaccine, and changes in disease activity can transiently reduce β-receptor expression or function[36-38] and thus influence the level of anaphylactic risk. This multiplicity of uncontrolled variables makes the susceptibility of individual patients to this potential adverse effect of β-blockers largely unpredictable.

Paradoxic treatment effects

Beta-blockade radically alters the pharmacotherapeutic actions of epinephrine and other adrenergic drugs normally used to treat acute anaphylaxis.[17,39] For example, it may be necessary to increase the usual intravenous dosage of iso-

proterenol as much as 80-fold to competitively overcome β-blockade.[40,41] Beta-blockers block the expected β_1- and β_2-antianaphylactic actions of epinephrine, thus facilitating unopposed α-adrenergic and reflex vagotonic effects, which can lead to augmented mediator release, bronchoconstriction and bradycardia.[17,39] Augmented release of mediators from the rich population of mast cells in cardiac tissue and atheromatous vessels may intensify the direct effects of anaphylaxis on the heart.[42] The unopposed α-receptor activation in the presence of excess epinephrine may also constrict coronary arteries[43] or dangerously exaggerate epinephrine's systemic pressor effects.[17-19]

Incidence

During 1985, 1.3 million prescriptions were filled in Canada for Inderal (Ayerst Laboratories, Montreal) alone — one nongeneric brand of the many β-blockers now marketed here (Pharmaceutical Manufacturers Association of Canada: personal communication, 1986) (Table I). Furthermore, the sales of β-blockers exceed those of any other category of cardiovascular drugs. This emphasizes the need for reliable data on the incidence of β-blocker-related anaphylaxis. However, these data do not exist, and while there is documentation supporting increased anaphylaxis severity,[1-8,10-12] it is still not known whether β-blockade also increases the clinical incidence of anaphylaxis.

The occurrence of five cases within 18 months in a suburban allergy practice[5] suggests that the association may be more frequent than is generally appreciated. Among 25 patients who presented consecutively to a university hospital with severe anaphylaxis, three were receiving β-blockers, and the reactions in these patients were about three times more likely to follow a protracted course than those in the other patients.[11] In only one study have investigators attempted to estimate the degree of relative risk.[33] This prospective study in nonconcurrent cohorts, carried out under the aegis of the Canadian Society of Allergy and Clinical Immunology (CSACI), revealed that the incidence of anaphylactic reactions to immunotherapy was higher in six patients receiving β-blockers than in six closely matched control subjects.[33] The likelihood of anaphylaxis during immunotherapy was three times greater when β-blocker therapy was given concurrently (odds ratio 3.09, relative risk 21/1000 injections) and seven times higher than the incidence in a large, unselected population receiving immunotherapy with similar antigens.[44] However, the numbers in the CSACI study are too small to provide a definitive estimate of relative risk. A large multicentre study is needed. Until such a study is completed, health care professionals should be aware of this possible risk and of the need for aggressive, prolonged support in patients who experience anaphylaxis while receiving β-blockers.

The anaphylactic reactions that occurred in patients receiving β-blockers in the CSACI study were mild and responsive to conventional anaphylaxis treatment, and most of the immunotherapy injections given during β-blocker therapy were tolerated without reaction. Thus, if an increase in incidence actually exists, factors other than β-blocker therapy per se must be important co-determinants of risk. As discussed in the section on pathogenesis, such factors vary among patients and may fluctuate with time, depending on the activity of the allergic process and other uncontrolled variables.

Because no reliable predictors of risk are known and because one cannot be sure that the risk can be materially reduced by resorting to a "cardioselective" drug, prevention must be the primary strategy in dealing with the problem. Allergy diagnosis and therapy constitute an area in which this strategy may usefully be applied. More than half a million treatment services for allergy are rendered annually in Canada by medical specialists and family practitioners, mostly the latter.[45] Thus, these physicians in particular should be aware of the need for preventive action.

Table I — Beta-blocker drugs currently available in Canada

Oral
Apo-Metoprolol (metoprolol tartrate)
Apo-Propranolol (propranolol hydrochloride)
Betaloc (metoprolol)
Blocadren (timolol maleate)
Corgard (nadolol)
Detensol (propranolol)
Inderal (propranolol)*
Lopresor (metoprolol)
Novopranol (propranolol)
Sotacor (sotalol hydrochloride)
Tenormin (atenolol)
Trandate (labetalol hydrochloride)
Trasicor (oxprenolol hydrochloride)*
Visken (pindolol)
Ocular
Betagan (levo-bunolol)
Betoptic (betaxolol)
Timoptic (timolol)
Combination products
Cobetaloc (metoprolol-hydrochlorothiazide)
Inderide (propranolol–hydrochlorothiazide)
Timolide (timolol–hydrochlorothiazide)
Viskazide (pindolol–hydrochlorothiazide)

*Available in sustained-release preparations (Inderal-LA and Slow-Trasicor).

Prevention

Allergy skin testing carries a small but definite risk of anaphylaxis in any patient. In patients receiving β-blockers for angina pectoris, withdrawal of the β-blocker to facilitate skin testing may

result in increased angina and myocardial infarction.[46] Slow withdrawal cannot be relied on to preclude this risk.[47] If allergy testing is clinically essential, an in-vitro method such as the radioallergosorbent test (RAST) may be preferable.

In patients receiving β-blockers who have allergic conditions that carry a low or negligible risk of death (e.g., allergic asthma or hay fever), prudence dictates that alternative forms of therapy — which are readily available, generally well tolerated and demonstrably effective — be used in preference to immunotherapy (Table II). On the other hand, anaphylactic sensitivity to Hymenoptera venom is a life-threatening allergic problem for which immunotherapy is known to be extremely efficacious and for which no reliable alternative preventive treatment exists. Beta-blocker therapy places such patients in double jeopardy whether venom immunotherapy is given or withheld. Furthermore, given the paucity of data, it is impossible to accurately estimate the degree of risk with one course of action relative to the other. The safest course would be to replace β-blocker therapy with an appropriate alternative and then institute venom immunotherapy.

Finally, the cautions and relative contraindications for β-blocker use currently listed in the package insert and in the compendium published by the Canadian Pharmaceutical Association for the use of health care professionals[21] should be expanded to include reference to patients prone to recurrent anaphylaxis, either idiopathic or due to an identifiable cause such as allergy to foods, insect stings, drugs, injectable biologicals, antigens and vaccines. This is particularly important given the broad range of diseases now treated with β-blockers in clinical practice: cardiac arrhythmias, hypertension, angina, myocardial infarction, hypertrophic subaortic stenosis, migraine, glaucoma, hyperthyroidism, essential tremor and pheochromocytoma.

Treatment

Patients who experience anaphylaxis while receiving β-blockers should be treated promptly with epinephrine, the standard first-line drug. It is rapidly effective in some cases.[33] An injectable H_1 antihistamine such as diphenhydramine hydrochloride should also be given. Adding an H_2 antihistamine is sometimes useful in anaphylaxis,[48] but cimetidine may be inadvisable with a β-blocker since it could decrease the clearance of the drug and, possibly, prolong its effect.[49] Salbutamol should be given by inhalation for bronchospasm, along with atropine if the bronchospasm is refractory. Intubation or oxygen administration or both may be needed to correct hypoxemia. Intravascular volume depletion should be treated with isotonic saline or colloidal solution; up to 10 L may be required, depending on the duration and severity of the shock. Military antishock trousers can be an effective adjunct.[6]

Persisting anaphylaxis should be treated with intravenous administration of isoproterenol or dopamine at dosages much higher than usual to competitively overcome the β-blockade. Dopamine is less effective for bronchodilation but is preferred in shock because of its combined α- and β-adrenergic activity. Intravenous administration of glucagon has been effective in patients with nonallergic shock caused by an overdose of β-blockers, which is unresponsive to β-agonists,[50-53] possibly owing to a direct effect of the glucagon on cyclic AMP in cardiac tissue independent of the β-receptor. It has been effective for anaphylactoid shock occurring with normal dosages of β-blockers[12] but may not be equally effective for bronchospasm.[51] Thus, its use in anaphylaxis remains controversial.[6,54] Intravenously given hydrocortisone has no effect on the early phases of anaphylaxis, and its value in averting late sequelae or extended reactions is problematic.[11] All patients should be monitored for several hours after apparent recovery from acute anaphylaxis in case of relapse or a two-phase reaction.[11]

Table II — Alternatives to immunotherapy in patients with low-risk allergic conditions who are receiving β-blockers

Alternative therapy	Condition	
	Allergic rhinitis	Asthma
Oral		
H_1-antihistamines	●	
Adrenergics	●	●
Theophylline		●
Steroids	●	●
Inhaled		
Topically active steroids	●	●
Cromoglycate	●	●
Anticholinergic agents		●

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